RESPIRATORY MEDICINE (1998) **92**, 597–598

Short Reports

Mycobacterium vaccae: a study of safety and outcome measures

O. M. KON*, M. GOYAL*, E FILLEY†, G. GLEISSBERG* D. CUNNINGHAM‡, G. A. W. ROOK AND R. J. SHAW*

*Department of Respiratory Medicine, Imperial College School of Medicine at St. Mary's Hospital. London, U.K.
†Department of Medical Microbiology, U.C.L. Medical School, London, U.K.
‡Directorate of Radiology, St. Mary's Hospital, London, U.K.

Background

Mycobacterium vaccae has been assessed as a potential immunotherapeutic treatment in tuberculosis (TB) (1–6) with apparent success. However, these trials were performed in centres where TB is severe, drug resistance is widespread, conventional therapy is not optimal and there is a relatively high mortality rate (7). As a prelude to further studies in a country where there is good response to standard chemotherapy and low mortality, a small double-blind, placebo-controlled study was undertaken to identify optimum indices of disease activity for use as outcome measures of efficacy and to assess the safety of *M. vaccae*.

Methods

Eleven patients (ten male, one female) with fully sensitive and bacteriologically proven active pulmonary TB participated (mean age, 40 years; range, 21–58 years). Six patients were randomized into the placebo group and five into the active group. All gave informed consent and the study was approved by the St. Mary's Local Research Ethics Committee.

This was a randomized double-blind, placebo-controlled study. Following diagnosis all subjects were started on conventional anti-tuberculous chemotherapy (rifampicin, isoniazid and pyrazinamide for 2 months followed by rifampicin and isoniazid for a further 4 months). From 1 to 2 weeks later, a single intradermal injection of 0·1 ml of *M. vaccae* or saline was given. Subjects were followed up by a 'blinded' physician and progress monitored by weight, chest radiographs, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) for a total of 4 months. In addition soluble interleukin-2 receptor (sIL-2R), the percentage of IgG that is of the agalactosyl glycoform [Ga1(0) I(%)] and concentrations of antibody to lipoarabinomannan (anti-LAM) were analysed.

Chest radiographs were reported on and graded according to a modification of the WHO guidelines (8) by a radiologist blinded to the treatment code. This score ranged from trivial changes (score 1) to extensive disease (score 8). sIL-2R was measured with a kit in accordance with the manufacturer's instructions (Medgenix diagnostics SA; code 40 027 00). Anti-LAM and Ga1(0) (%) measurements were performed as described previously with minor modifications (9).

Results

All patients who received active treatment tolerated the injection of *M. vaccae* well. Two subjects had a small, localized pustular reaction at the site of injection which resolved spontaneously over 72 h. There were no systemic reactions and no long-term scarring. One subject in the active group suffered from a myocardial infarction after 12 weeks but this was not felt to be related to the immunotherapy.

With the exception of two subjects from the placebo group, all patients had an increase in their weight. The median gain in the active group was 4·2 kg (range 1·8–10 kg) and placebo 6·15 kg (range −2·5 kg to +8·2 kg). All subjects demonstrated a decrease in ESR with a median fall in the active group of 24 mm h^{-1} (range 14–64 mm h^{-1}) and in the placebo group 19 mm h^{-1} (range 1–57 mm h^{-1}). There was an improvement in CRP concentrations in all subjects (Fig. 1) with a median reduction in the active group of 30 mg l^{-1} (range 0–99 mg) l^{-1} and in the placebo group of 31·5 mg l^{-1} (range 0–106 mg l^{-1}). Individuals with the highest initial CRP concentrations tended to have abnormal concentrations at 16 weeks but improvements were more clearly seen in these patients. The results for CRP exhibited the least fluctuation when results

Received 10 February 1997 and accepted in revised form 4 August 1997.
Correspondence should be addressed to: R. J. Shaw, Department of Respiratory Medicine, Imperial College School of Medicine at St. Mary's Hospital, Praed Street, London W2 1PG, U.K.

0954-6111/98/030597+02 $12.00/0

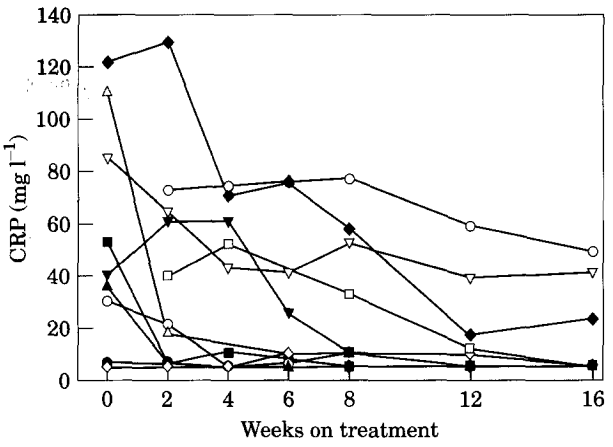

FIG. 1. Changes in CRP (mg l^{-1}) over 16 weeks in individual patients: open symbols, placebo ($n=6$); full symbols, *M. vaccae* ($n=5$).

from all parameters were compared. With the exception of one subject, there was an improvement in sIL-2R concentrations in all patients with a median reduction in the active group of 410 units ml^{-1} (range 72–1179 units ml^{-1}) and the placebo group 906 units ml^{-1} (range+299 to −1327 units ml^{-1}). There was a median improvement in chest radiograph scores in the active group of 1·0 (range 0–4) and in the placebo group of 1·5 (range 0–6). There was no consistent change in the level of Gal(0) (%) and anti-LAM.

As the majority of patients were unable to produce sputum after treatment we were unable to assess the rate of change in sputum positivity. Furthermore, two subjects had only been diagnosed after either a bronchoalveolar lavage or after sputum culture at 5 weeks.

There were no significant differences in the changes of the parameters measured, between active and placebo groups. Significant correlations were noted between the chest radiograph score and ESR ($r=0·46$, $P=0·03$), CRP ($r=0·57$, $P=0·005$) and sIL–2R ($r=0·61$), $P=0·003$) but not between the change in weight and these parameters.

Discussion

In this small study, *M. vaccae* appeared to be well tolerated and did not produce any serious adverse effects.

We also observed that surrogate markers of disease activity are unsatisfactory. Although there was a trend to improvement in the parameters measured there was a high noise-to-signal ratio and we were unable to demonstrate any statistically significant difference between treatment groups. There appeared to be a good correlation between the inflammatory markers and chest radiograph scores although this could not be demonstrated for the changes in weight.

This study illustrates the problems of studies in the developed world in establishing outcome measures to assess the efficacy of novel treatments of TB in the context of effective chemotherapy.

References

1. Pozniak A, Stanford JL, Grange JM. *Mycobacterium vaccae* immunotherapy. *Lancet* 1991; **338:** 1533–1534.
2. Onyebujoh PC, Abdulmumini T, Robinson S, Rook GAW, Stanford JL. Immunotherapy with *Mycobacterium vaccae* as an addition to chemotherapy for the treatment of pulmonary tuberculosis under difficult conditions in Africa. *Respir Med* 1995; **89:** 199–207.
3. Stanford JL, Bahr GM, Rook GAW *et al.* Immunotherapy with *Mycobacterium vaccae* as an adjunct to chemotherapy in the treatment of pulmonary tuberculosis. *Tubercle* 1990; **71:** 87–93.
4. Stanford JL, Onyebujoh PC, Rook GAW, Grange JM, Pozniak A. Old plague, new plague and a treatment for both? *AIDS* 1993; **7:** 1275–1277.
5. Etemadi A, Farid R, Stanford JL. Immunotherapy for drug-resistant tuberculosis. *Lancet* 1992; **340:** 1360–1361.
6. Corlan E, Marica C, Macavei C, Stanford JL, Stanford CA. Immunotherapy with *Mycobacterium vaccae* in the treatment of tuberculosis in Romania. 1. Newly-diagnosed pulmonary disease. *Respir Med* 1997; **91:** 13–19.
7. Kochi A. The global tuberculosis situation and the new control strategy of the World Health Organization. *Tubercle* 1991; **72:** 1–6.
8. Simon G. Radiology in epidemiological studies and some therapeutic trials. *Br J Med* 1966; **2:** 491–494.
9. Rook GAW, Onyebuyoh P, Wilkins E *et al.* A longitudinal study of percent agalactosyl IgG in tuberculosis patients receiving chemotherapy, with or without immunotherapy. *Immunology* 1994; **81:** 149–154.